CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH
SUMMARY OF TOXICOLOGY DATA
PROPANIL
Chemical Code # 000503, Tolerance # 00274
SB 950 # 829

July 23, 1998
Revised: 10/26/99, 8/14/00, 1/29/03

I. DATA GAP STATUS

Chronic/Onco, Rat	No data gap, possible adverse effect
Chronic toxicity, dog:	No data gap, possible adverse effect
Oncogenicity, mouse:	No data gap, possible adverse effect
Reproduction, rat:	No data gap, no adverse effect.
Teratology, rat:	No data gap, no adverse effect.
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	Data gap, inadequate study, no adverse effect
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

All record numbers through 182114 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.

File name: T030129
Updated by: J. Kishiyama & M. Silva, 7/23/98; M. Silva, 10/26/99, 8/14/00, 1/29/03

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

**** 018 132825**, "Propanil Technical, Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Rats", (M.E. Bellringer, Huntingdon Research Centre, Study No. PTF 3, 7/1/94). Propanil (purity = 96.5-98.5%) was fed in diet to Crl:CD(SD)BR rats (50/sex/dose) at 0, 200, 600 or 1800 ppm for 104 weeks and to 20/sex/dose for 52 weeks. **Chronic NOAEL** = 200 ppm (Incidence of discolored incisors were increased in females at 1800 ppm. Body weight decreased 13% & 23% (M) and 20% & 45% (F) at 600 & 1800 ppm, respectively. Food consumption was decreased intermittently in both sexes at $\geq$ 600 ppm. PCV, RBC and Hb values were intermittently significantly decreased in females at $\geq$ 200 ppm throughout the study and were significantly decreased in males at $\geq$ 600 ppm through week 52. Methemoglobin values were increased for both sexes at $\geq$ 600 ppm and also intermittently in females at 200 ppm. Bilirubin and urea nitrogen levels were intermittently increased in both sexes at 1800 ppm. Triglycerides were reduced in both sexes at $\geq$ 600 ppm. Spleen weight was increased in both sexes at $\geq$ 600 ppm. Liver weights (F) and testes + epididymide weights were increased at 1800 ppm. Enlarged spleen ($\geq$ 600 ppm, M; 1800 ppm, F), congested dark spleen (1800 ppm, M & F), and testicular masses ($\geq$ 600 ppm) were observed grossly. Livers in both sexes showed increased granulomatous inflammation, pericholangitis, brown pigmented Kupffer cells, bile duct hyperplasia, eosinophilic and/or basophilic hepatocytes and centrilobular and/or generalized hepatocyte enlargement at $\geq$ 600 ppm. Testicular focal interstitial hyperplasia and marked tubular atrophy were observed at 1800 ppm. Increase in absent spermatozoa, reduced secretion and prostate atrophy occurred at $\geq$ 600 ppm. Hemosiderin was observed in the spleen and kidneys of both sexes at $\geq$ 600 ppm.) **Possible adverse effect:** Testicular interstitial cell tumors and hyperplasia were increased at 1800 ppm. Females showed increased hepatocullular adenomas at 1800 ppm. ACCEPTABLE (Kishiyama & Silva, 2/4/98).

ONCOGENICITY, MOUSE

**** 019 134723**: "24-Month Dietary Oncogenicity Study with Propanil," (Tompkins, E.C., WIL Research Laboratories, Inc., WIL-141011; 9/9/94). Propanil (purity = 97%) was fed in diet to Crl:CD-1®(ICR)BR mice (80/sex/dose) for 104 weeks at 0, 500 and 1000 ppm (M: 74.9 & 150 mg/kg/day; F: 88.6 & 174.1 mg/kg/day). Twenty/sex/dose were sacrificed at 52 weeks. Chronic NOEL < 500 ppm/day (There was an increase in clinical signs in both sexes at $\geq$ 500 ppm. Body weights and food consumption were significantly decreased throughout the study in both sexes at 1000 ppm. Methemoglobin and reticulocyte count were increased and RBC was decreased at 1000 ppm. Mean corpuscular volume (both sexes at 1000 ppm) and incidence in Heinz Bodies (males at $\geq$ 500 ppm) were also affected. Females had significantly increased absolute and relative spleen weights at interim sacrifice at 1000 ppm. Weights remained increased at termination, although not significantly when compared to control.) NOEL = 500 ppm/day: **Possible adverse effect:** increased

incidence of malignant lymphoma and methemoglobinemia and Heinz Bodies. ACCEPTABLE. (Kishiyama & Silva, 2/27/98).

CHRONIC TOXICITY, DOG

**** 016 129293**, "One Year Oral Toxicity Study in Dogs with Propanil", (E.C. Tompkins, WIL Research Laboratories, Inc., WIL-141007, 9/29/93). Propanil (purity = 96.9-98.5%) was fed in diet to Beagle dogs (4/sex/dose) at 0, 200, 1600 or 3200 ppm for 12 months. NOEL < 200 ppm (Clinical findings increased (soft stool, decreased defecation and urination and increased mucoid feces in females), primarily at ≥ 1600 ppm. Food consumption and body weight gain were decreased in both sexes at 3200 ppm. Absolute and relative liver and thyroid/parathyroid weights were increased in both sexes and thymus weights were decreased in both sexes at 3200 ppm. Several hematological changes (increased methemoglobin and Heinz bodies and decreased mean RBC, hemoglobin and hematocrit) in both sexes, observed at all doses, indicated hemolysis and methemoglobinemia were occurring. At all dose levels there was increased hemosiderosis (liver, kidney and bone marrow), observed in both sexes.) NOAEL = 200 ppm/day. **Adverse effect: hematology (reduced RBC and Hb) and microscopic (hemosiderin of the kidneys) changes were apparent for mid and high dose groups and to a lesser extent for the low dose group.** ACCEPTABLE. (Kishiyama & Silva, 2/23/98).

REPRODUCTION, RAT

** 065 162957 "A Dietary Two-Generation Reproductive Toxicity Study of Propanil in Rats," (Stump, D.G., WIL Research Laboratories, Ashland, OH; Study #: WIL-141013; 7/1/98). Propanil (purity = 98.4% aliquot #6 & 98.3% aliquot #7) was fed in diet to Sprague-Dawley Crl:CD®BR (30/sex/dose/generation) at 0, 60, 150 and 600 ppm for 2 generations (pre-mating F0 through weaning of F2). Parental Systemic NOEL = 150 ppm (F0 females showed an increased occurrence of hair loss at 600 ppm. F0 & F1 adults of both sexes showed decreased body weights at 600 ppm. During gestation and lactation F0 & F1 female body weights were significantly decreased at 600 ppm. F0 showed significantly increased food consumption (g/kg/day) throughout the study. F0 & F1 females at 600 ppm showed significantly decreased food consumption throughout gestation and lactation. F0 & F1 spleen weights were significantly increased in females at 600 ppm. F0 relative right testes weights and relative brain weights (both sexes) were significantly increased at 600 ppm. Relative female F0 ovary and adrenal glands were significantly increased at 600 ppm. F1 absolute liver and kidney weights were significantly decreased at 600 ppm in both sexes. F1 males showed significantly increased relative (to body) brain, kidney, seminal vesicle/coagulating gland, both testes, left cauda epididymus, adrenal gland and spleen weights at 600 ppm. Relative F1 brain, spleen, ovaries and adrenal glands were increased in females at 600 ppm. F1 liver weights were decreased in both sexes at 600 ppm. Female F1 relative weights for liver and pituitary were decreased and spleen weights were increased at 600 ppm. Both sexes of both generations showed increased spleen pigmented macrophages at 600 ppm (dose-related increase in severity). Reproduction NOEL = 150 ppm (The left epididymus showed decreased sperm count at 600 ppm in F0 & F1. The F1 left testis showed decreased sperm count at 600 ppm.) Pup NOEL = 150 ppm (F1 weanling males at 600 ppm showed significantly increased relative testes and liver weights. There

was a significant increase in age in F1 at balanopreputial separation observed in males at 600 ppm.) Acceptable. No adverse 042 152692 AThree Generation Reproduction Study on Rats Receiving Stam F-34 in Their Diet,@ (Borzelleca, J.F., Ambrose, A.M. & Larson, P.S., Department of Pharmacology, Medical College of Virginia, VA; Report #: 66RC-1048; 2/7/66). Stam F-34 (Propanil; Lot #: 9315; concentration not specified) was fed in diet to Wistar rats (25/sex/dose) for 11 weeks at 0, 100, 300 and 1000 ppm. Subsequently, 20/sex/dose (F0 parental generation) were mated to produce the F1a generation. This procedure was used for 3 generations (2 litters/generation). Not acceptable (No effects at any dose in any generation. An MTD was not achieved.) Not upgradeable (Too many missing parameters. The study was performed prior to FIFRA Guidelines.) M. Silva, 7/23/98.

TERATOLOGY, RAT

** 026, 070 138206, 166892 "Original Study: Teratological Evaluation of Stam Technical in the Albino Rat; Supplemental: Snell Project 310065-008: Evaluation of Stam Technical in the Albino Rat (Teratology Study)," (Original Study: Gallo, M.A., Rohm and Haas Company, Toxicology Dept., Snell Project #10065-008; Rohm and Haas Company Report #: 81RC-027B; 2/29/80; Supplemental Study: The Propanil Task Force (c/o McDermott, Will & Emery), Washington, DC; 2/1/99). Stam Technical (purity = 85.4%) was administered by gavage at 0 (corn oil), 0.8, 4, 20 and 100 mg/kg to mated Sprague -Dawley rats (20/dose) during gestation days 6 through 15. Maternal NOEL = 100 mg/kg/day. Developmental NOEL = 100 mg/kg/day (Minimal effects were observed as decreased fetal weights at 100 mg/kg but they were not statistically significant.) Acceptable, based on submitted rangefinding/dose justification data. No adverse effect. (M. Silva, 8/10/00).

069 166727 This volume is an exact duplicate of 070 166892. M. Silva, 8/10/00.

041 152689 Duplicate of 026 138206.

TERATOLOGY, RABBIT

** 027, 070 138207, 166895 "Stam Technical Teratogenicity study in Rabbits, Report Supplement: Rohm and Haas Report NO. 81RC-015B," (Original Report: Florek, C.M.; Argus Research Laboratories, Inc., Argus Project 018-001, Rohm and Haas Report No. 81RC-015; 12/17/80; Supplement: O'Neill, P.J.; Rohm and Haas Company, Toxicology Dept., Spring House, PA; 6/4/93). Stam Technical (purity = 85.4%) was administered to artificially inseminated New Zealand white rabbits (20/dose) by gavage at concentrations of 0 (corn oil), 4, 20 and 100 mg/kg/day (approximately 4.7, 23.4 & 117.1 mg/kg/day) during gestation days 6 through 18. Maternal mortality was 25% at 100 mg/kg/day. Maternal NOEL = 20 mg/kg/day (There was increased mortality and decreased body weight observed at 100 mg/kg/day.) Developmental NOEL >100 mg/kg/day (There were no significant fetal effects observed at any dose.) This study is now complete and has been upgraded to acceptable. M. Silva, 8/10/00.

069 166728 This volume is an exact duplicate of 070 166895 M. Silva, 8/10/00

041 152691 Duplicate of 027 138207.

GENE MUTATION

014 112966, "Mutagenicity of Chloroaniline/Lignin Metabolites in the *Salmonella*/Microsome Assay," (K.A. Rashid, M. Arjmand, H. Sandermann & R.O. Mumma, Journal of Environmental Science Health, B2(6), 721-729 [1987]). 3,4-DCA, a metabolite of propanil, was used at 0, 1, 10, 100 and 1000 ug/plate (+/- S-9 metabolic activation) on *Salmonella typhimurium* strains TA98 and TA100. No evidence of mutagenicity was observed is this study. No repeat study was performed. Inadequate number of *Salmonella* strains tested and insufficient information. UNACCEPTABLE, not upgradeable. (no worksheet). These data are supplemental. (Kishiyama & Silva, 2/ 11/98).

** 025 138205: "Microbial Mutagenicity Test of DCPA Propanil," (Shirasu, Y., Moriya, M. and Koyashiki, R.; Toxicology Division, Institute of Environmental Toxicology; February 14, 1980). Propanil (purity = 98%) was used at 0, 20, 100, 200, 500, 1000, and 2000 : g/disk with *B. subtilis* strains (H17 and M45) in a rec assay and at 0, 1, 5, 10, 50, 100, 500, 1000, and 5000 : g/plate (+/- S-9) with *Salmonella typhimurium* strains (TA1535, TA1537, TA1538, TA98 & TA 100) in reversion assays and *Escherichia coli* strain WP2 *hcr* in reversion assays, to test for DNA damage. No evidence of mutagenicity was observed in any test. ACCEPTABLE. No adverse effect. (Kishiyama & Silva, 2/6/98).

** 022 138202 "Stam® Technical CHO/HGPRT Gene Mutation Assay," (Kruszewski, F.H., K.L. McCarthy, and M.J. Byers; Report No. 83R-142; January 12, 1984). Stam7 Technical (purity = 87.8%) was evaluated at 0, 15, 75, 125 or 150 : g/ml (no S-9; 18-20 hour exposure or 0, 100, 115, 130 or 140 ug/ml (with S-9; 5 hour exposure) for mutagenic activity in Chinese ovary (CHO) cells. No adverse effects (There was no increase in mutagenic activity using the CHO test system). ACCEPTABLE. (Kishiyama & Silva, 2/4/98).

CHROMOSOME EFFECTS

** 274 - 091 182113 "Mammalian Erythrocyte Micronucleus Test," (Gudi, R., Krsmanovic, L.; BioReliance Laboratory, Rockville, MD; Study #: AA36HB.123.BTL; 6/5/01). Propanil technical (97.1% pure) was administered to ICR mice (5/sex/dose/time point) in a single intraperitoneal injection at 0 (corn oil), 100, 200, 400 mg/kg. At 24 hours post-dosing, 5/sex/dose were sacrificed for all doses, including cyclophosphamide (positive control, 50 mg/kg) and control. At 48 hours post-dosing, 5/sex/dose at 0 and 400 mg/kg were sacrificed. After treatment, 1/15 females died at 400 mg/kg. Clinical signs observed on the days following dosing included: lethargy and piloerection in both sexes at 100, 200 and 400 mg/kg (all doses). In addition, prostration and irregular breathing in both sexes and crusty eyes in females were observed at 400 mg/kg. There was no treatment-related increase in micronuclei at any dose. ACCEPTABLE (some deficiencies). (Kishiyam & Silva, 1/29/03).

023 138203: "Stam(pede) Cytogenetic Study in Mice," (O=Neil, P.J., P.L. McLeod, K.L. McCarthy; Rohm & Haas Company, Toxicology Dept.; Report No. 82R-255, November 11, 1983). Stampede Technical (87.8% pure) was administered p.o. in a single dose to male Charles River CD-1 mice (24/dose)at 0 (corn oil), 26.5, 106, and 265 mg/kg. Bone marrow slides (chromosomal

evaluation) were prepared from eight animals/group/sacrifice scheduled at 6, 24, and 48 hours post-dosing. An additional 8 animals/dose were treated po daily for five days and were sacrificed 6 hours after the final dose. A decrease in spontaneous motor activity was observed at ≥ 106 mg/kg. At 265 mg/kg, lethargy was observed on Day 1. Piloerection was observed at ≥ 106 mg/kg. NOEL = 26.5 mg/kg (Decreased motor activity, lethargy and piloerection occurred at ≥ 106 mg/kg. There was no increase in chromosomal aberration.) Not acceptable (Only one sex was tested without justification.) (Kishiyama & Silva, 2/11/98).

DNA DAMAGE

274 - 092 182114 "Unscheduled DNA Synthesis in Mammalian Cells *In Vitro,*" (San, R.H.C., Reece, J.D.; BioReliance, Rockville, MD; Laboratory Study Number AA36HB.380.BTL; 6/5/01). Propanil technical (purity = 97.1%) was used on primary rat hepatocytes at 1.0, 5.0, 25, 50 and 100 μg/ml to evaluate the potential for induction of unscheduled DNA synthesis *in vitro* with autoradiography (3 replicates/dose; 1 trial). Propanil technical, at doses tested, did not significantly increase the incidence in unscheduled DNA synthesis. No adverse effect. The study is currently unacceptable but is possibly upgradeable with submission of data for nuclear and cytoplasmic grain counts for each coverslip. (Kishiyama & Silva, 1/29/03).

024 138204 "*IN VITRO* Microbiological Mutagenicity and Unscheduled DNA Synthesis Studies of Eighteen Pesticides," (Simmon, V.F., SRI International, Menlo Park, CA; 10/79). In this study, propanil (88%) was used at 10, 50, 100, 500, 1000, and 5000 : g/plate with and without metabolic activation (S-9) in a mutagenicity assay with *Salmonella typhimurium* (TA1535, TA1537, TA1538, TA98 and TA100) and *Escherichia coli (WP2).* Propanil was toxic to *S. typhimurium* strains at 1000 : g/plate and did not increase histidine revertants at any dose level tested in three experiments. Propanil did not increase tryptophan revertants in a test with *E. coli (WP2).*
In another assay, Propanil was tested *in vitro* at concentrations from 0.01 to 5.0% (+/- S-9) using *Saccharomyces cerevisiae* (D3). Propanil at ≥ 1.0% (+/- S-9) was toxic to the test organism. Propanil did not significantly increase mitotic recombination at the doses used in two experiments. Propanil was also tested at 0.1 to 1000 : g/ml (+/- S-9) using human fibroblasts (WI-38 cells). Precipitation was observed at 1000 : g/ml. Increases in ^{3}HTdR incorporation were not observed at tested doses. **Unacceptable (insufficient details and data reporting). Not upgradeable.** (Kishiyama & Silva, 2/9/98).

NEUROTOXICITY

Not required at this time.